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Chronic polyneuropathy of undetermined cause

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SUMMARY The case histories of 519 patients with peripheral neuropathy on whom sural nerve biopsy had been performed were reviewed. In 67 patients (50 males, 17 females) (13%) who had symptoms of a symmetrical polyneuropathy for more than one year, the cause remained undiagnosed in spite of intensive investigation. Patients with inflammatory neuropathy were not included, but represented 17% of the whole series. The mean age of onset of symptoms was 50·6 years, and the median time from onset of symptoms to initial investigation was 2 years. Males were affected more commonly than females in a ratio of 3:1. The clinical features in 43 patients were those of a mixed motor and sensory neuropathy, in 17 patients a predominantly sensory neuropathy and in 7 patients a predominantly motor neuropathy. The mean CSF protein was 0·73 g/l and in only six patients was it greater than 1 g/l. Nerve conduction studies most commonly demonstrated mild slowing of motor conduction and impairment of sensory conduction. The usual pathological changes on sural nerve biopsy were those of chronic axonal degeneration.

Forty seven patients (70%) were re-examined at intervals of time which ranged from 4 months to 12 years after their initial presentation and nerve biopsy (median, 3 years). As a group, they were only mildly disabled, the condition had a very slowly progressive course and there had been little change in their disability. A possible aetiological factor was found in 17 of the 47 patients (36%) and included malignancy, alcoholism, and benign paraproteinaemia. It is concluded that with intensive investigation the cause of chronic polyneuropathy of duration greater than one year remains undetermined in only about 13% of patients and that continued follow-up is worthwhile since a diagnosis may be established on re-examination.

The present study was undertaken in order to establish the proportion of cases in which a diagnosis could not be made in a series of patients with peripheral neuropathy who were subjected to intensive investigation including sural nerve biopsy, and to describe the clinical, pathological and electrophysiological features of these cases. A further aim of the study was to follow up patients with chronic neuropathy of undetermined cause to ascertain whether aetiological factors subsequently became apparent on re-evaluation.

It has been variously estimated that 24–70% of cases of peripheral neuropathy remain undiagnosed.[1 2 3 4] However, many of the previous studies included cases of acute and chronic inflammatory neuropathy which are now regarded as specific entities with a probable immune basis.

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Materials and methods

Our department is responsible for providing a regional service for peripheral nerve biopsies in the state of New South Wales, which has a population of 5·2 million people. The case histories of 519 patients in whom there was adequate clinical information available and who had been referred to our department for sural nerve biopsy during the years 1967 to 1981 were reviewed. Of these, 138 (27%) patients had a genetically determined neuropathy (hereditary motor and sensory neuropathy (HMSN) types I and II, Friedreich's ataxia and other spinocerebellar degenerations, hereditary sensory neuropathy, Dejerine-Sottas disease, severe axonal neuropathy of childhood, metachromatic leukodystrophy); 88 (17%) had inflammatory neuropathy (27 acute and 61 chronic); 226 (43%) had acquired neuropathies of different types (alcoholic, nutritional, diabetes, carcinoma, lymphoma, multiple myeloma and other dysproteinaemias and paraproteinaemias, toxic neuropathies due to drugs, arsenic, gold and thallium, lep-

rosy, vitamin B12 deficiency, liver disease, chronic renal failure, rheumatoid arthritis, polyarteritis nodosa, systemic lupus erythematosus and primary amyloid disease).

In the remaining 67 cases (13%), all of whom had symptoms of a symmetrical polyneuropathy for more than one year, no cause was found at the initial assessment which usually included the following investigations: haemoglobin, white cell count, erthrocyte sedimentation rate (ESR), liver function tests, antinuclear antibody and LE cells, serum B12, serum and red cell folate, blood urea, serum creatinine, porphyrin screen, blood sugar, glucose tolerance test, serum lipids and lipid EPG, serum protein EPG, serology for syphilis, heavy metal screen, thyroid function studies, bone marrow examination and chest x-ray. Not all these studies were necessarily indicated on every patient, but were performed on the majority.

Electrophysiological studies were performed in all cases at initial presentation and in most cases at follow-up examination. The techniques employed for motor and sensory conduction studies are standard in our laboratory and have been described elsewhere.[5] Motor conduction velocities were determined in the median, ulnar and lateral popliteal nerves. Supramaximal stimuli were applied to each nerve at two sites, and muscle action potentials were recorded through surface electrodes or concentric needle electrodes from the abductor pollicis brevis, abductor digiti minimi, and extensor digitorum brevis muscles, respectively. Sensory action potentials were recorded through surface electrodes from the median and ulnar nerves at the wrist on stimulating the index and little fingers, respectively. The mixed nerve action potential was recorded through surface electrodes from the ulnar nerve above the elbow on stimulating at the wrist and from the lateral popliteal nerve at the neck of the fibula with needle electrodes on stimulating at the ankle.

Sural nerve biopsy was performed on all patients at the initial assessment. Techniques were similar to those previously employed and have been described in detail elsewhere.[5] Sural nerve biopsy was performed at the level of the lateral malleolus. A portion of nerve was fixed in Flemming's solution for 24–36 hours, dehydrated in alcohol, embedded in paraffin wax, and cut transversely in serial section of 5 μm thickness. The sections were stained with Kultschitsky hematoxylin and counter-stained with van Gieson stain. Photographs of selected fascicles were prepared and enlarged to a final magnification of $\times 1000$. The external diameter of these fibres was measured using a Zeiss TGZ3 Particle Size Analyser set in the linear mode. Fascicular area was measured with a planimeter, and fibre density was expressed as the number of fibres per mm^2 of intraperineurial area.

A second piece of nerve was fixed in formol saline and then stained for 24 hours in 1% osmium tetroxide. Single fibres were isolated and examined.

A third piece of nerve was fixed in cold 3% glutaraldehyde in 0·1 M cacodylate for three hours followed by Dalton chrome-osmium for 90 minutes. The tissue was dehydrated in graded concentrations of ethanol, passed through acetone, and embedded in araldite. Sections were cut with glass or diamond knives and double-stained with uranyl acetate and lead citrate and examined in a Philips 200 or 201 electron microscope.

Follow-up studies The records of all patients were carefully reviewed and attempts were made to contact all for follow-up studies. Forty seven patients were clinically reviewed and the remaining 20 patients could not be contacted.

The disability status of the patients was graded as follows[3]: 0 = normal, 1 = signs but not symptoms or vice versa, 2 = mild motor and/or sensory symptoms including sensory ataxia, 3 = moderately disabled by motor or sensory symptoms including sensory ataxia, 4 = requiring assistance in eating, dressing or using a walking aid, 5 = not ambulant.

Statistics Means are expressed with standard deviations. Where data are not normally distributed median values and ranges are given.

Results

CLINICAL FEATURES

Of the 67 patients studied, there were 50 males and 17 females. The age of onset of symptoms was 12–73 years (mean 50·6, SD 14·1). The time from onset of symptoms to initial investigation ranged from one to 54 years (median 2 years). The clinical features were those of a sensorimotor neuropathy in 43 patients, predominantly sensory neuropathy in 17 patients, and predominantly motor neuropathy in 7 patients. The characteristic history was that of a gradual onset of numbness, tingling, coldness or burning sensation in the feet and hands; heaviness and weakness of the legs and less commonly weakness of the hands. Neurological examination demonstrated distal muscle wasting and weakness in the lower limbs in two-thirds of the patients, in some cases quite pronounced with bilateral foot drop. In all except two patients, the ankle jerks were absent and in about one-third of patients both knee and ankle jerks were absent. Total areflexia was less common. There was distal sensory impairment to light touch and painful sensation and impaired position and vibration sense, more pronounced in the lower limbs, in most cases.

Cerebrospinal fluid (CSF) protein

Lumbar puncture was performed on 44 patients. The CSF protein ranged from 0·1 to 8 g/l (mean 0·73, SD 1·18). In only 6 patients was the CSF protein greater than 1 g/l; of these 4 were subsequently found to have a malignancy, one was ultimately found to have total lipodystrophy,[6] and in the other, no cause was determined.

Electrophysiological studies

The results of motor and sensory conduction are summarised in the table. Electrophysiological studies were performed on all patients, although not all nerves were always studied. Compared with con-

Table *Nerve conduction studies in chronic polyneuropathy of undetermined cause*

Subjects	*Motor conduction velocity*			*Median SAP*		*Ulnar SAP*	
	Median nerve (ms^{-1})	*Ulnar nerve* (ms^{-1})	*Peroneal nerve* (ms^{-1})	*Latency* (ms)	*Amplitude* (μv)	*Latency* (ms)	*Amplitude* (μv)
Chronic polyneuropathy* (age 22–78)							
Mean ± SD	49·4 ± 9·2	49·5 ± 12·5	40·5 ± 5·6	3·6 ± 5·6	4·3 ± 5·8	3·6 ± 0·6	2·7 ± 3·5
Range	33–63	16–70	28–52	2·6–4·8	0–23	2·2–4·1	0–16
Controls (age 18–73)							
Mean ± SD	56·9 ± 5·0	55·7 ± 4·6	47·3 ± 4·9	3·0 ± 0·3	17·9 ± 7·5	2·5 ± 0·3	13·7 ± 6·4
Range	49–66	47–69	38–56	2·2–3·8	9–40	2·0–3·4	5–36
Significance (Student t test)	$p < 0·001$	$p < 0·01$	$p < 0·001$	$p < 0·001$	$p < 0·001$	$p < 0·001$	$p < 0·001$

*Age at which conduction studies performed.

trols, motor conduction was significantly slower in the median, ulnar and lateral popliteal nerves and sensory action potentials in the median and ulnar nerves were reduced in amplitude and prolonged in latency. Abnormalities were demonstrated in all but 2 patients. In only 4 patients was the motor conduc-

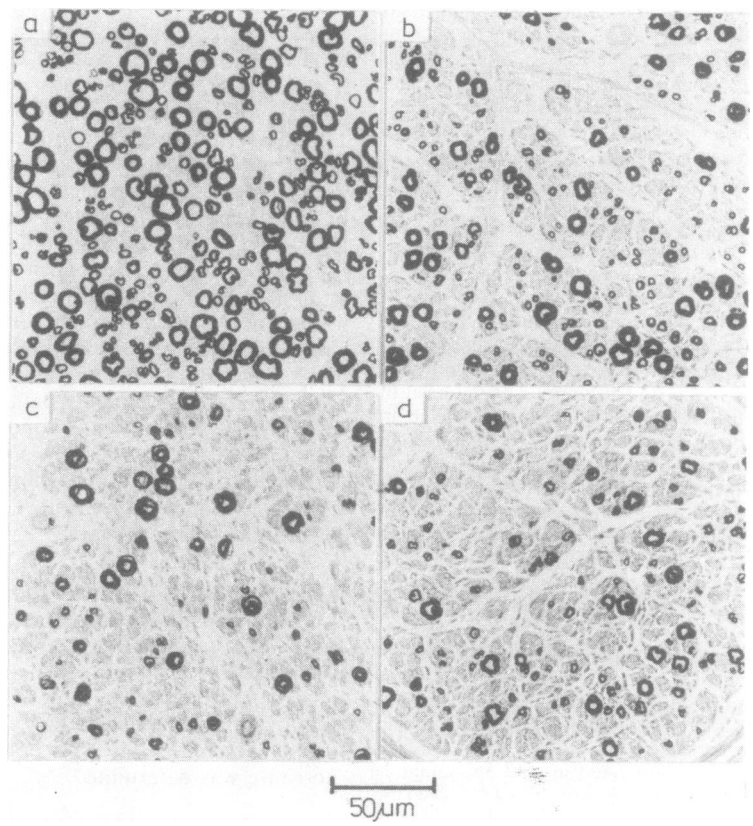

Fig 1 *Photomicrographs of sections of sural nerves of a. Control patient. b. case 70–15, aged 62, with chronic sensorimotor neuropathy for 2 years. c. case 74–63, aged 66, with chronic sensorimotor neuropathy for 2 years; carcinoma of lung diagnosed 4 years later. d. case 79–58, aged 43, with 5 years history of sensorimotor neuropathy. Flemming-Kultchitsky-haematoxylin.*

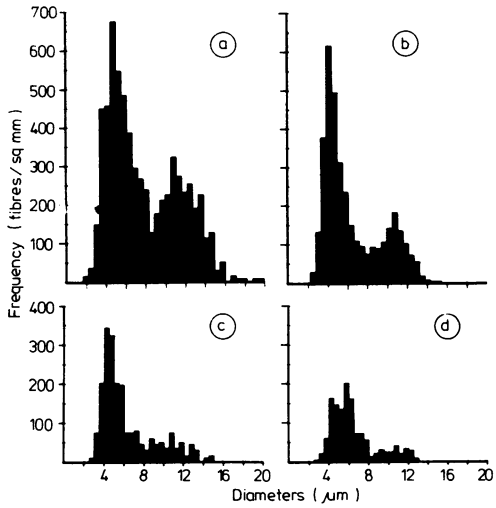

Fig 2 *Distribution of myelinated fibre diameters in sural nerves of same patients as in Fig 1.*

tion velocity in one or more nerves reduced to values that suggested a demyelinating neuropathy (less than 40 ms^{-1} in median or ulnar nerves and less than 30 ms^{-1} in the lateral popliteal nerve).[7]

HISTOPATHOLOGICAL STUDIES

No specific features were seen on haemotoxylin and eosin stained sections; there was no evidence of arteritis, inflammation or infiltration. In most cases there was a generalised loss of myelinated fibres affecting all diameters (fig 1, 2). The density of myelinated fibres ranged from 0 to $5{\cdot}98 \times 10^3$ fibres/mm^2 (mean 3·14, SD 1·50) which may be compared with the control range of $3{\cdot}81$ to $6{\cdot}42 \times 10^3$ fibres/mm^2 (mean 4·57, SD 0·89) in our laboratory.[5] On teased fibre studies axonal degeneration and regeneration were the usual findings and segmental demyelination was rarely present. On electron microscopy the characteristic findings were generalised loss of myelinated fibres with cluster formations indicating regeneration following axonal

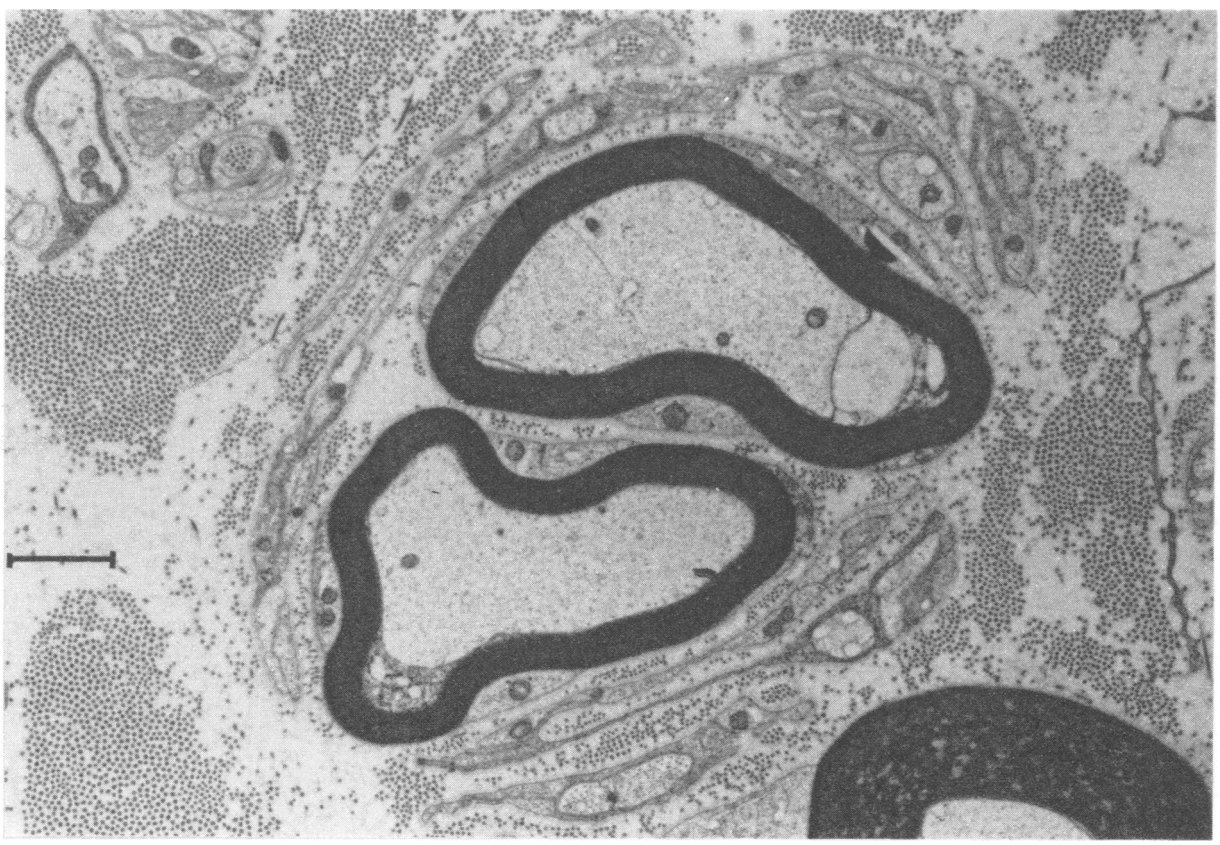

Fig 3 *Electromicrograph of sural nerve of case 74–55 aged 68 with 10 year history of sensorimotor neuropathy showing typical cluster formation. Bar = 2 μm.*

degeneration (fig 3). Morphometric studies were not performed on unmyelinated fibres.

FOLLOW-UP STUDIES

Forty seven patients (70%) were reviewed at intervals of time which ranged from 4 months to 12 years after their initial presentation and nerve biopsy (median 3 years). The median interval from onset of symptoms to final review was 5 years. The mean disability at the time of biopsy in this group of patients was 2·5 (SD, 0·8) and at review 2·6 (SD, 1·1). Clearly as a group there had been little change; 4 patients had improved, 9 had become worse and the rest remained unchanged.

At review a possible aetiological factor was determined in 17 of the 47 patients (36%). Five patients were found to have developed a malignancy (carcinoma of the lung 2, carcinoma of the pancreas 1, seminoma of the testis 1, carcinoma of the colon 1), 6 patients were found to be alcoholic even though excess alcohol had been specifically denied at the initial evaluation, 1 had total lipodystrophy,[6] 1 had systemic lupus erythematosus, 1 was found to have hereditary sensorimotor neuropathy type 1, and 3 patients were found to have a benign paraproteinaemia (IgM lambda paraprotein in 2 patients and IgA Kappa paraprotein in 1 patient). In patients with malignancy the duration of symptoms at initial investigation and biopsy had ranged from 6 months to one year.

Discussion

In the present study in which the diagnosis of 519 patients with peripheral neuropathy referred for sural nerve biopsy was analysed, it was found that 67 (13%) cases with chronic symmetrical polyneuropathy had experienced symptoms for more than one year and, after full investigation, the condition remained undiagnosed. Patients with acute and chronic inflammatory neuropathy were not included in this latter group but represented 17% of the whole series. There is no entirely satisfactory definition of chronic inflammatory neuropathy, or chronic inflammatory polyradiculoneuropathy, a term used by Dyck and co-workers[8] to describe a condition with subacute onset and a steadily progressive, chronic monophasic or recurrent course in which there is often a preceding infection or exposure to foreign protein, a tendency to involve cranial, truncal and proximal as well as distal limb structures and to have diffusely slow conduction velocities in peripheral nerves. The CSF protein is usually elevated. It is the same condition as that of subacute and relapsing idiopathic demyelinating neuropathy described by others.[9 10 11] In the present study, patients with these clinical features, marked slowing of conduction, raised CSF protein and prominent demyelination in the sural nerve biopsy, have been excluded; however, it is possible that some atypical cases of chronic inflammatory neuropathy may have been included and the few patients with marked slowing of nerve conduction possibly fall into this category.

In the series of 205 patients referred to the Mayo Clinic for evaluation of peripheral neuropathy, 24% remained undiagnosed and 21% had inflammatory neuropathy. Allowing for differences in referral patterns and selection of case material (all our patients had sural nerve biopsies), the figures are similar to our own. Prineas[3] analysed 278 cases with polyneuropathy at Newcastle-Upon-Tyne. One hundred and seven of these patients were classified as idiopathic but included patients with acute and inflammatory neuropathies. When these were excluded only 38 patients (14%) were found to have a chronic polyneuropathy of undetermined cause, which may be compared to the proportion of 13% in our own series. The findings are in contrast to those of Fagius[12] who found that the underlying cause could not be determined in 74% of 91 patients with chronic polyneuropathy. However, sural nerve biopsy was not performed and patients with chronic inflammatory and hereditary neuropathy may have been included.

Chronic polyneuropathy of undetermined cause, no doubt a heterogeneous group of conditions, has a male preponderance; in the present study the ratio of males to females was close to 3:1 and in the series reported by Prineas[3] it was 2:1. The onset in most patients was in the fifth or sixth decade which again is very similar to the finding of Prineas.[3] A mixed sensorimotor neuropathy is the usual clinical feature but predominantly motor and sensory neuropathies also occur. Very few patients were severely disabled (only nine in category 4 or 5) and the condition progressed very slowly over many years in most instances. Only 4 patients improved, and in one case recovery was found to be due to alcohol abstention. Electrophysiological studies and sural nerve biopsy indicate that in most cases the underlying pathology is that of a chronic axonal degeneration. The CSF protein is not greatly elevated in most cases and when it exceeds 1g/l the likelihood of associated malignancy or other systemic disease is high.

We are not aware of previously published follow-up studies on patients with chronic polyneuropathy of undetermined cause. We were able to review 47 of the 67 patients at a median interval of 3 years after the initial sural nerve biopsy was performed. In 17 of the patients a possible aetiological factor was revealed and it is of interest

that underlying malignancy, which was not apparent at the initial investigation, became manifest in five. Six patients were found to be chronic alcoholics and it is likely that covert alcoholism is a significant factor in some patients with the condition, possibly accounting for the age of onset and male preponderance. It is also probable that some patients with predominantly motor and mixed sensory neuropathies may be sporadic cases of hereditary neuropathies, especially HMSN type 2, which does not have distinctive histological features; patients who had the characteristics features on sural nerve biopsy of HMSN type 1[13] were excluded from the study. Dyck and co-workers[4] found that inherited disorders accounted for 42% of their series of undiagnosed neuropathies and in over one third of the cases the diagnosis was established only be careful examination of relatives. In our study examination of relatives was performed in the 138 (27%) of patients with genetically determined neuropathy, but was not possible in all the patients with chronic peripheral neuropathy of undetermined cause. If the 17 cases in which a possible aetiological factor was finally revealed at follow-up were excluded, only 50 patients, or 10% of the total number of 519 patients on whom sural nerve biopsy was performed, remained undiagnosed.

In conclusion, the present study has demonstrated that with modern intensive methods of investigation the cause of chronic polyneuropathy of duration greater than one year remains undetermined in only 13% of cases referred to a specialized neurological centre. Most of the patients with chronic polyneuropathy of undetermined cause have a chronic axonal degeneration and the condition is usually not disabling and only very slowly progressive. It is likely that those remaining undiagnosed are a heterogeneous group including unrecognized alcoholic, nutritional and genetically determined neuropathies. Follow-up studies of such cases are worthwhile since a probable aetiological factor was thus revealed in approximately one-third of our cases.

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